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AUTHOR(S):

Shimabukuro, Tomoyuki; Nakamura, Kanehiro; Uchiyama, Kouichi; Tei, Yasuhide; Aoki, Akihiko; Naito, Katsusuke

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ANGIOTENSIN-II COMBINED INTRA-ARTERIAL CHEMOTHERAPY FOR LOCALLY ADVANCED BLADDER CANCER : A CASE SERIES STUDY AT A SINGLE INSTITUTION

Tomoyuki SHIMABUKURO[1,2], Kanehiro NAKAMURA[2], Kouichi UCHIYAMA[2], Yasuhide TEI[2], Akihiko AOKI[2] and Katsusuke NAITO[3]

[1]*The Department of Urology, Ube Industries Central Hospital*
[2]*The Department of Urology, Masuda Red Cross Hospital*
[3]*The Department of Urology, Yamaguchi University School of Medicine*

Patients with locally advanced bladder cancer are at significant risk for metastases. We aimed to evaluate the usefulness of intra-arterial chemotherapy (IAC) combined with angiotensin-II (AT-II) in such patients. The possibility of bladder preservation is also discussed.

Patients were enrolled if they had muscle-invasive bladder cancer (stage T2 to T4NxM0). Cisplatin, pirarubicin, and AT-II were infused through the tumor-feeding arteries. Cause-specific survival was the end point.

We enrolled 37 patients who were treated with neoadjuvant IAC and 5 patients with adjuvant IAC. There were 7 patients (16.7%) with pathological complete remission. Overall 5-year and 10-year survival rates of the patients were 61.3% and 47.7%, respectively. The 5-year cause-specific survival rate was 100% for the clinical T2 group and 63% for the T3-4 group, and the 8-year survival rate was 33% and 63%, respectively. There was no statistically significant difference between these two groups ($P=0.445$). Multivariable analysis using tumor number, pattern of growth, and tumor size seemed to independently correlate with cause-specific survival, but there were no significant differences.

Our results suggest that intra-arterial chemotherapy combined with AT-II is a useful treatment for patients with locally advanced bladder cancer, since this modality achieves a favorable response rate without severe toxicity or mortality.

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Key words : Bladder cancer, Muscle-invasion, Intra-arterial chemotherapy, Angiotensin-II, Prognosis

INTRODUCTION

Bladder cancer is a worldwide problem related to tobacco use. In Japan, it is the seventh most common cancer. Some 43,000 cases were expected in Japan in 2002 with an estimated 5,100 deaths. Although radical cystectomy remains the ideal treatment in Japan for muscle invasive bladder cancer, this disease is one of the most aggressive cancers with a high rate of early systemic dissemination. Treatment failure is usually due to occult systemic disease already present at diagnosis. Cystectomy series gave 5-year survival rates after cystectomy of 36% to 54%[1-4]. For high-risk cases of pT3 to pT4 and/or pN+M0 bladder cancer 5-year survival is only 25% to 35%.

Following neoadjuvant intra-arterial chemotherapy (IAC), bladder preservation may be possible in some selected cases[5,6] Bladder preservation in the patient with locally advanced bladder cancer means less surgery, no need for a urinary diversion and a normal sexual life. These factors are important in determining the quality of life. If there is any possibility of bladder preservation this chance should not be missed.

According to our previous preliminary report[7], we aimed to evaluate the usefulness of IAC combined with angiotensin-II (AT-II) in patients with locally advanced bladder cancer, and the possibility of bladder preservation is discussed.

METHODS

Patients

From January 1988 to December 1997, 42 patients who consulted Masuda Red Cross Hospital and were diagnosed with locally advanced bladder cancer (stages T2 to 4NxM0) were enrolled in this study and retrospectively analyzed for the efficacy of IAC combined with AT-II. In principle, all patients with locally advanced bladder cancer were indicated for this study. Diagnostic and staging classification procedures including tumor cup biopsy, a chest radiograph, excretory urogram, ultrasonography, abdominal-pelvic computerized axial tomography (CT), magnetic resonance imaging (MRI), bone scans, and evaluation of treatment efficacies were conducted in accordance with the General Rules for Clinical and Pathological Studies on Bladder Cancer edited by Japanese Urological

Association and the Japanese Society of Pathology[8] The clinical stage of disease was T2 (cT2) in 8 patients, cT3 in 24 and cT4 in 10. Histological diagnosis was pure transitional cell carcinoma (TCC) in 34 patients and variant (TCC plus squamous cell carcinoma or adenocarcinoma) in 8. No patient had received prior radiotherapy or chemotherapy. Thirty-seven patients did not yet have histologically proven muscle invasive disease treated with neoadjuvant IAC and 5 patients were initially diagnosed with cT1 disease before transurethral resection of bladder tumor (TURBT) with adjuvant IAC. TURBT of the tumor site(s) was done by wide and deep resection.

All patients were informed regarding the nature of this treatment.

Angiotensin-II Combined Intra-arterial Chemotherapy

After performing pelvic arteriography by the Seldinger method under local anesthesia and visualizing the courses of the bilateral internal iliac arteries and tumor-feeding arteries, two 4Fr catheters were inserted through the bilateral femoral arteries, and advanced and fixed with the tips around the bifurcation of the superior gluteal arteries. Cisplatin (100 mg per body weight per infusion), pirarubicin (30 mg per body weight per infusion), and AT-II (20 μg per body weight per infusion) were infused in principle during approximately 15 minutes while monitoring the blood pressure. The treatment schedule was repeated 2 to 3 times in principle by evaluating the tumor size at 3 to 4 week intervals to allow for recovery from toxicity.

The efficacies of treatment against the tumors were evaluated 4 weeks after the IAC by pathological evaluation. Wide and deep TURBT of the tumor site or segmental cystectomy was performed on the patients in whom the tumor disappeared completely to confirm the complete absence of viable tumor cells. Patients with residual tumor underwent either 2nd TURBT, segmental cystectomy, radical cystectomy or radiotherapy according to their medical conditions, age, performance status, and their own decision.

Follow-up examination for the patients with functional bladder preservation included cystoscopy and washing urine cytology studies every 3 months for 2 years and every 4 to 6 months thereafter.

All procedures were performed at the Department of Urology and Radiology, Masuda Red Cross Hospital.

Statistical Analysis

The overall and cause-specific survival for all patients treated by neoadjuvant or adjuvant IAC, and for subgroups of patients classified by pretreatment clinical stage and histologic subtype was analyzed using Kaplan-Meier method, and statistically treated using log-rank and Breslow-Gehan-Wilcoxon tests. Survival was measured from the time of the first intra-arterial chemotherapy. Proportional-hazards models were used to adjust for covariates and to evaluate interaction terms in which cause-specific survival was the end point. All analyses were by intention to treat.

A probability (P) value of <0.05 was considered statistically significant and all P values reported were two-sided.

RESULTS

Patient Characteristics

Between January 1988 and December 1997, 42 patients with muscle-invasive bladder cancer (cT2 to 4 NxM0) were treated with intra-arterial chemotherapy. Thirty-seven patients were treated with neoadjuvant IAC and 5 patients with adjuvant IAC. There were 3 patients with 1 cycle of IAC, who refused to continue the second schedule, 17 with 2 cycles, and 22 with 3 cycles. Thirty-one patients (74%) were men and eleven (26%) were women. The median age of the neoadjuvant IAC group was 74 years (range 52 to 86) and that of the adjuvant IAC group 75 years (range 63 to 80). Baseline

Table 1. Baseline characteristics of the patients

Characteristic	Neoadjuvant IAC (%) (n=37)	Adjuvant IAC (%) (n=5)
Age: yr		
Median (range)	74 (52–86)	75 (63–80)
Sex		
Male	26 (70.3)	5 (100)
Female	11 (29.7)	0 (0.0)
Disease Stage		
T2	6 (16.2)	2 (40)
T3	22 (59.5)	2 (40)
T4	9 (24.3)	1 (20)
Macroscopic Appearance		
Number		
Single	17 (45.9)	4 (80)
Multiple	20 (54.1)	1 (20)
Pattern of growth		
Papillary, pedunclated	2 (5.4)	0 (0.0)
Papillary, sessile	9 (24.3)	4 (80)
Non-papillary, sessile	25 (67.6)	1 (20)
Unknown	1 (2.7)	0 (0.0)
Size (cm)		
<3.0	12 (32.4)	3 (60)
>3.0	25 (67.6)	2 (40)
Microscopic Appearance		
Architecture		
TCC	29 (78.4)	5 (100)
TCC>SCC	6 (16.2)	0 (0.0)
TCC>AC	2 (5.4)	0 (0.0)
Grade		
Grade 2	19 (51.4)	0 (0.0)
Grade 3	13 (35.1)	5 (100)
Unknown	5 (13.5)	0 (0.0)

TCC denotes transitional cell carcinoma, SCC squamous cell carcinoma, and AC adenocarcinoma.

Table 2. Response to intra-arterial chemotherapy

Response	Neoadjuvant IAC (%) (n=37)	Adjuvant IAC (%) (n=5)
CR	6 (16.2)	1 (20.0)
PR	27 (73.0)	—
NC	4 (10.8)	—
ND	—	4 (80.0)

IAC denotes intra-arterial chemotherapy, CR pathological complete remission, PR pathological partial remission, NC no change, and ND no determination.

characteristics of the patients are shown in Table 1. The median follow-up period was 64 months (range 4 to 130) for the neoadjuvant group and 43 months (range 8 to 126) for the adjuvant group.

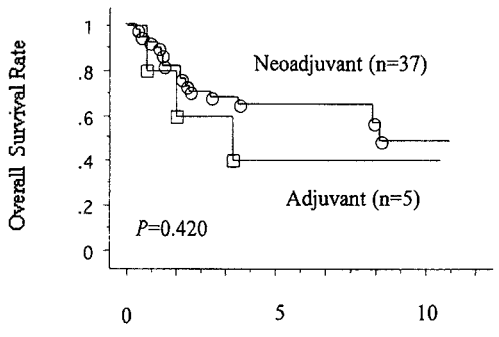
Response and Survival

Responses to IAC are shown in Table 2. Overall 5-year and 10-year survival rates of the patients treated with IAC were 61.3% and 47.7%, respectively.

Fig. 1 shows the overall survival of the patients treated with neoadjuvant or adjuvant IAC. For all 42 patients with locally advanced bladder cancer, the 5-year survival rate was 64.5% for the neoadjuvant group and 40.0% for the adjuvant group, and the 10-year survival rate was 48.4% and 40.0% , respectively. There was no statistically significant difference between these two groups (P=0.420).

In addition, the overall 5-year survival rate was 33.3% for the 1-cycle IAC group, 64.2% for the 2-cycle IAC group, and 62.9% for the 3-cycle IAC group. There was no statistically significant difference between these three groups.

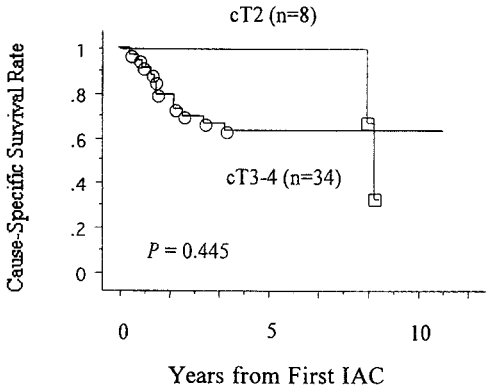
Cause-specific survival by pretreatment clinical stage for the 42 patients who were treated with IAC is shown in Fig. 2. In cT2 group, there were 3 deaths, 2 of them due to distant metastases, and one of unknown cause. For all 42 patients with locally advanced bladder cancer,



No. at Risk

Neoadjuvant	37	19	1
Adjuvant	5	2	1

Fig. 1. Overall survival of patients who received neoadjuvant or adjuvant intra-arterial chemotherapy (IAC).



No. at Risk

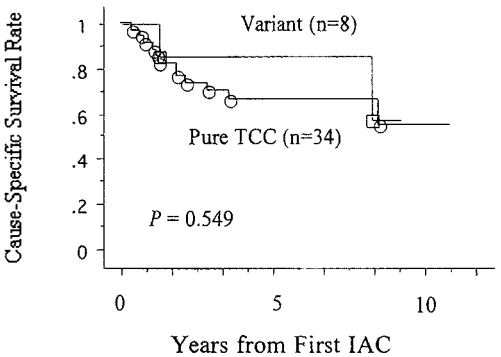
cT2	8	6	0
cT3-4	34	15	2

Fig. 2. Cause-specific survival according to clinical T (cT) stage of patients who received neoadjuvant or adjuvant intra-arterial chemotherapy (IAC).

the 5-year survival rate was 100% for the cT2 group and 63% for the cT3-4 group, and the 8-year survival rate 33% and 63%, respectively. The 10-year survival rate for the cT3-4 group was 63% There was no statistically significant difference between these two groups (P=0.445).

Fig. 3 shows the cause-specific survival by histological subtype for the 42 patients treated with IAC. For all 42 patients with locally advanced bladder cancer, the 5-year survival rate was 66% for the pure TCC group and 86% for the variant group; and the 9-year survival rate 55% and 57%, respectively. The 10-year survival rate for pure TCC group was 55% There was no statistically significant difference between these two groups (P=0.549).

Fig. 4 shows the cause-specific survival by response



No. at Risk

TCC	34	15	2
Variant	8	6	0

Fig. 3. Cause-specific survival according to histological subtype. Pure TCC denotes pure transitional cell cancer, and variant denotes TCC plus other subtypes.

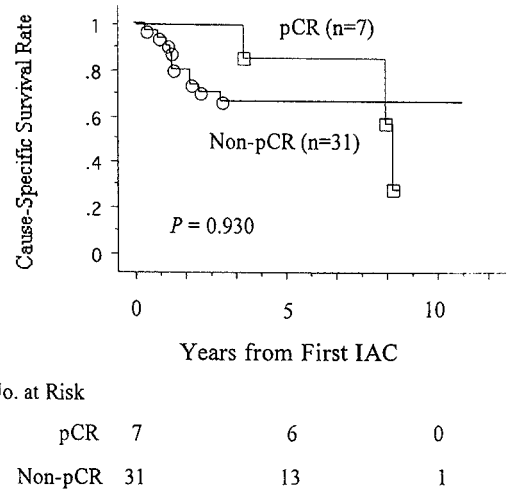


Fig. 4. Cause-specific survival according to pathological response. pCR denotes pathological complete remission.

group. There were 7 patients with pathological CR (pCR) or 31 patients with non-pCR by IAC. In the pCR group, there were 3 deaths due to distant metastases and 4 survivors, 3 of them with no evidence of local recurrence, and one with local recurrence. The 5-year survival rate was 86% for the pCR group and 66% for the non-pCR group, and 8-year survival rate 29% and 66%, respectively. The 10-year survival rate for the non-pCR group was 66%. There was no statistically significant difference between these two groups (P= 0.930).

Univariable hazard ratio of cause-specific death from locally advanced bladder cancer treated with neoadjuvant IAC revealed that the variables of tumor number, pattern of growth, and tumor size seemed to correlate with survival. Multivariable analysis using these variables is shown in Fig 5. Tumor number and pattern of growth independently tended to correlate with cause-specific survival, but there were no statistically significant differences.

Toxicity

Toxicities of IAC are shown in Table 3. No patients died of IAC or postoperative complications or were too ill to undergo IAC. All toxicity criteria were grade 2 or less, and all patients tolerated IAC well. All symptoms except pedal neurological pain were immediately relieved after IAC. The pedal pain (17%) persisted for several months after IAC.

Surgery or Other Treatment Modalities

The treatment modalities except IAC are shown in Table 4. Our study did not reveal any obvious increase in perioperative morbidity after IAC.

DISCUSSION

Intra-arterial chemotherapy (IAC) is a treatment modality designed to obtain a high concentration of anticancer agents at the tumor site to enhance their effectiveness. In a previous report, we demonstrated that the theoretical cisplatin concentration infused by IAC combined with AT-II of the responding group was significantly higher than that of the non-responding group (P=0.01)[7] Stewart et al. reported that the serum level of an agent following intra-arterial administration is the same as that after intravenous

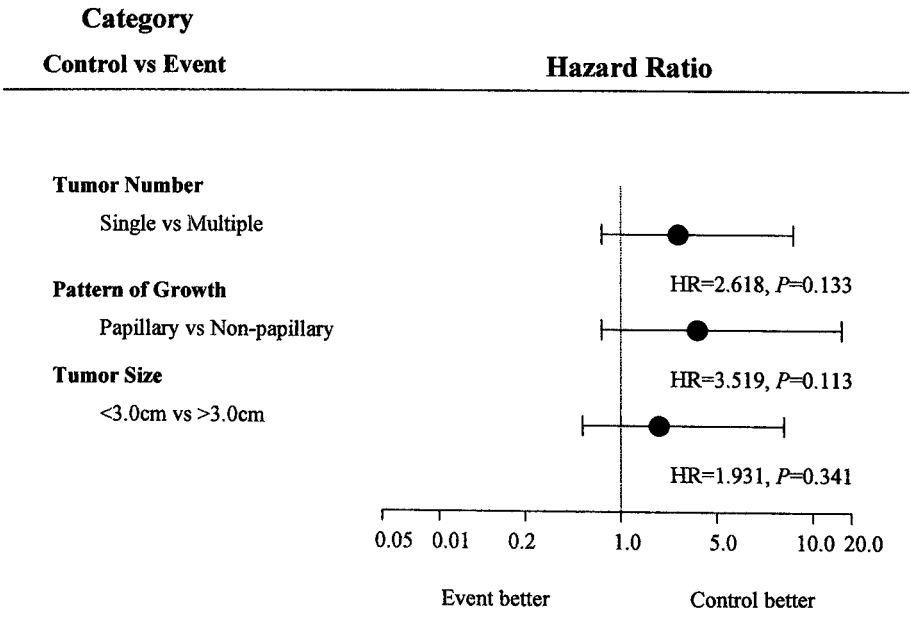


Fig. 5. Multivariable hazard ratio plots for cause-specific death from locally invaded bladder cancer treated with neoadjuvant intra-arterial chemotherapy (n = 37). Data markers indicate hazard ratio for control versus each event; lines indicate extent of 95% confidence intervals. HR denotes hazard ratio.

Table 3. Toxicity of intra-arterial chemotherapy

Toxicity	Patients (%)
Blood/Bone marrow	
Leukopenia	12 (28.6)
Gastrointestinal	
Nausea/Vomiting	8 (19.1)
Neurology	
Pedal Pain	7 (16.7)
Constitutional symptoms	
Fever	2 (4.8)
Faintness	1 (2.4)
Genitourinary	
Bladder irritability	1 (2.4)
Cardiovascular	
Hypotension	1 (2.4)
Pain	
Headache	1 (2.4)

Table 4. Surgical or other treatment modalities

Modality	Neoadjuvant IAC (%) (n=37)	Adjuvant IAC (%) (n=5)
TURBT	20 (54.1)	5 (100)
Segmental cystectomy	3 (8.1)	—
Radical cystectomy	1 (2.7)	—
Radiation therapy	3 (8.1)	—
Miscellaneous	10 (27.0)	—

IAC denotes intra-arterial chemotherapy, TURBT transurethral resection of bladder tumor.

administration[9] This finding is important because the IAC regimen is effective not only for local lesions but also for distant microscopic metastases. Based on these findings, we combined the use of cisplatin and pirarubicin, because these agents are definitively effective against urothelial cancers, and their activities are dose-dependent. With respect to AT-II, which we used as a vasoactive drug, Sasaki et al. stated that AT-II contracts normal vessels but does not contract tumor vessels due to the lack of autoregulation of the blood flow in tumor tissues[10] In the present study, we also added AT-II to increase the intra-tumor concentrations of these anti-cancer agents.

The response to IAC is summarized in Table 2. The pathological complete response (pT0; no evidence of disease after surgical restaging) rate in the present study was 16.2% and pathological partial response (the presence of residual disease at operation) rate 73.0%, and clinical response rate approximately 90%. The pT0 rate was 33% in the European Organization for the Research and Treatment of Cancer/Medical Research Council (EORTC/MRC) international trial of neoadjuvant cisplatin (C), methotrexate (M) and vinblastine (V) chemotherapy, 38% in the United States Southwest Oncology Group (SWOG) trial and likewise, after 2 cycles of neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy 40% in the MD Anderson trial[11-13] In the present study the clinical response rate was comparable, but the pT0 rate was lower than these intravenous neoadjuvant chemotherapies. Galetti et al. treated 27 patients with invasive TCC of the bladder (T3 to 4NxM0 disease) with cisplatin and doxorubicin intra-arterially, and cyclophosphamide intravenously, or cisplatin alone intra-arterially. In a total of 19 patients underwent cystectomy after chemotherapy, they reported pathological complete response was observed in 26.3%, surgical complete response (the presence of residual disease at operation that could be completely resected) in 47.4% and pathological partial response (the residual disease could not be completely resected) in 26.3%[5] Sumiyoshi et al. reported a pT0 rate of 60% after intra-arterial doxorubicin chemotherapy in combination with low-dose radiotherapy[6]. The suggested reasons for our low pT0 rate compared to those reported by others are as follows : (1) we included all patients even if who received 1-cycle IAC, (2) relatively lower dosage of cisplatin and pirarubicin, (3) without combination with radiotherapy. To achieve the same pT0 rate with contemporary neoadjuvant therapy, we are now attempting to combine radiotherapy.

Cystectomy series gave 5-year survival rates after cystectomy of 36% to 54%[1-4] The EORTC/MRC trial of neoadjuvant CMV chemotherapy before cystectomy or definitive radiation therapy gave a 5-year survival of 50% and 8-year survival of 43%[14]. In the present study, for all 42 patients with locally advanced bladder cancer, the 5-year and 10-year overall survival rates of the patients treated with IAC were 61.3% and 47.7% , respectively. This clinical response rate is comparable to that in previous reports. Cause-specific survivals stratified by pre-treatment clinical stage, histological subtype, and clinical response did not show any statistically significant difference in any group (Fig. 2, 3 & 4). Additionally, there was no independent cause for cancer death identified in patients with locally advanced bladder cancer treated with neoadjuvant IAC by univariable or multivariable analyses (Fig. 5). Also in the cT2 or pCR group, there were cancer deaths due to distant metastases developing during the long follow-up period. Because bladder cancer is one of the most aggressive cancers with a high rate of early systemic dissemination, these findings emphasize the need for a better systemic control of the disease.

In the EORTC/MRC international trial of neoadjuvant CMV chemotherapy, the mortality was 1%[11] In the SWOG trial there were no deaths attributable to M-VAC[12] In the present study, although relatively older patients were enrolled, almost all were able to tolerate to IAC. The toxicity and mortality were favorable, but pedal neurological pain persisted for a longer period and impaired the quality of life of the patients (Table 3).

Bladder preservation influences quality of life since it

means less surgery, no need for a urinary diversion and a normal sexual life. After neoadjuvant therapy bladder preservation may be possible in highly select responding patients. The pT0 rate was 33% in the EORTC/MRC trial, 38% in the SWOG trial and 40% in the MD Anderson trial, respectively[11-13] In our present neoadjuvant IAC study, the pT0 rate was 16.2%. Although our pT0 rate was low, many of our patients desired bladder preservation. After obtaining their informed concent about the risks of multiple invasive procedures and uncertainty of tumor relapse, and their agreement to make frequent follow-up visits, we treated the patients trying to preserve their bladder (Table 4).

We are now attempting to combine IAC with locoregional radiotherapy to improve the efficacy of treatment and patient survival.

CONCLUSIONS

Locally advanced bladder cancer is a significant cause of morbidity and mortality, but is a chemosensitive disease. Neoadjuvant chemotherapy may be useful in programs of bladder preservation, but this approach has not been universally accepted[15-17] It remains a controversial topic since radical cystectomy is still regarded as the gold standard. Our results suggest that intra-arterial chemotherapy combined with AT-II is a useful treatment for patients with locally advanced bladder cancer, since this modality has a favorable response rate without severe toxicity or mortality.

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和文抄録

局所進行性膀胱癌に対する Angiotensin-II 併用動脈内注入化学療法：単独施設における症例集積研究

島袋　智之[1,2]，中村　金弘[2]，内山　浩一[2]
鄭　　泰秀[2]，青木　明彦[2]，内藤　克輔[3]
[1]宇部興産中央病院泌尿器科，[2]益田赤十字病院泌尿器科，
[3]山口大学医学部特殊専門領域腫瘍病態学講座（泌尿器科学）

局所進行性膀胱癌を有する患者は，遠隔転移のリスクが有意に高いことが知られている．そのような患者に，angiotensin-II（AT-II）併用動脈内注入化学療法を施行してその有用性を評価するとともに，併せて膀胱温存の可能性について考察した．

臨床病期 T2-T4NxM0 の膀胱癌を有する患者に，cisplatin，pirarubicin，AT-II を腫瘍栄養動脈より注入し，その治療効果を評価した．腫瘍特異的生存率を end point とした．

ネオアジュバント療法群37例とアジュバント療法群5例を対象とした．その中7例（16.7%）に病理学的完全寛解を認めた．全体の5年および10年生存率はそれぞれ61.3%と47.7%であった．臨床病期 T2 症例における5年および8年腫瘍特異的生存率は100%，33%であり，T3-4 症例ではそれぞれ63%，63%であった．両群間に推計学的に有意差は認められなかった（$P=0.445$）．単変量および多変量解析の結果，腫瘍数，増殖型，腫瘍の大きさが腫瘍特異的生存率と独立して相関傾向があったが，推計学的有意差は認めなかった．

今回の検討から，AT-II 併用動脈内注入化学療法は，重篤な副反応や合併症を伴わず，比較的良好な治療効果を有し，局所進行性膀胱癌患者に対する有用な治療法と思われた．

（泌尿紀要 **52**：99-105，2006）